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Associations between *TCF7L2* polymorphisms and risk of breast cancer among Hispanic and non-Hispanic White women: the Breast Cancer Health Disparities Study

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Abstract

The transcription factor 7-like 2 (*TCF7L2*) gene is part of the Wnt/β-catenin signaling pathway and plays a critical role in cell development and growth regulation. *TCF7L2* variants rs12255372 and rs7903146 have been associated with risk of Type 2 diabetes. Few epidemiological studies have examined the association between *TCF7L2* and breast cancer risk. We investigated the associations between 25 *TCF7L2* single nucleotide polymorphisms (SNPs) and breast cancer in Hispanic and non-Hispanic white (NHW) women from the 4-Corner's Breast Cancer Study, the San Francisco Bay Area Breast Cancer Study, and the Mexico Breast Cancer Study. A total of 4,703 Hispanic (2,093 cases, 2,610 controls) and 3,031 NHW (1,431 cases, 1,600 controls) women were included. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated using logistic regression to estimate the association between the *TCF7L2* SNPs and breast cancer risk. We also examined effect modification by self-reported ethnicity, genetic admixture, and diabetes history. After adjusting for multiple comparisons, four *TCF7L2* SNPs were significantly associated with breast cancer overall: rs7903146 (OR_{TT} 1.24; 95 % CI 1.03–1.49), rs3750805 ($OR_{AT/TT}$ 1.15; 95 % CI 1.03–1.28), rs7900150 (OR_{AA} 1.23; 95 % 1.07–1.42), and rs1225404 (OR_{CC} 0.82; 95 % 0.70–0.94). Among women with a history of diabetes, the TT genotype of rs3750804 increased breast cancer risk (OR, 2.46; 95 % CI 1.28–4.73). However, there was no association among women without a diabetes history (OR, 1.06; 95 % CI 0.85–1.32). We did not find significant interactions by ethnicity or by genetic admixture. Findings support an association between *TCF7L2* and breast cancer and history of diabetes modifies this association for specific variants.

Keywords

Breast cancer; Hispanic; Transcription factor 7-like 2; Polymorphisms; Type 2 diabetes

Introduction

The transcription factor 7-like 2 (*TCF7L2*) gene codes for a high mobility group (HMG) box transcription factor. Located on chromosome 10q, *TCF7L2* is part of the Wnt/β-catenin signaling pathway and plays a critical role in cell development and growth regulation [1]. TCF7L2 protein is involved in blood glucose homeostasis and gene variants rs12255372 and rs7903146 are reported to be associated with risk for Type 2 diabetes [2–4]. The mechanism for this association is uncertain; however, evidence indicates that the gene may regulate glucagon-like peptide 1 (GLP-1) through the Wnt-signaling pathway [5]. *TCF7L2* also regulates transcription of the proglucagon gene in enteroendocrine cells. In vitro, the proglucagon gene is responsible for the insulinotropic hormone GLP-1 [5]. The dominant negative *TCF7L2* variant is reported to repress proglucagon gene mRNA expression and subsequent GLP-1 synthesis [5]. Although results are mixed, some suggest that the *TCF7L2* gene may play a role in obesity [6, 7].

The *TCF7L2* gene plays a role in the Wnt/β-catenin pathway, which is reported to be associated with human carcinogenesis [8], and specifically with breast cancer [9, 10]. While, mutations within the Wnt pathway are rare in breast cancer, there is evidence for hyperactive signaling, especially in triple negative [estrogen receptor (ER), progesterone receptor (PR), and HER2 negative] or basal-like breast cancers [11–14]. Few epidemiological studies have investigated the association between *TCF7L2* and breast cancer risk [15–17]. We investigated the associations between 25 *TCF7L2* single nucleotide polymorphisms (SNPs) and breast cancer risk in Hispanic and non-Hispanic white (NHW) women. We also evaluated potential interactions between menopausal status and obesity, and tested for effect modification by ethnicity, genetic admixture, and history of Type 2 diabetes. In addition, we examined associations by tumor ER and PR status.

Methods

The Breast Cancer Health Disparities Study (BCHDS) is comprised of participants from three population-based case–control studies: the 4-Corner's Breast Cancer Study (4-CBCS), the San Francisco Bay Area Breast Cancer Study (SFBCS), and the Mexico Breast Cancer Study [18]. All participants signed informed written consent prior to participation; the study was approved by the Institutional Review Board for Human Subjects at each institution.

The 4-CBCS consisted of NHW and Hispanic/Native American women aged 25–70 years residing in Arizona, Colorado, New Mexico, and Utah at the time of diagnosis or selection. Cases newly diagnosed with in situ or invasive breast cancer between October 1999 and May 2004 were identified through the state-wide cancer registries [19]. A total of 852 Hispanic, 22 American Indian, and 1,683 NHW breast cancer cases completed an in-person interview in English or Spanish on breast cancer risk factors and participated in the measurement of height and weight. Controls under the age of 65 years were randomly selected from commercial mailing lists in Arizona and Colorado and driver's license lists in New Mexico and Utah. Controls 65 years of age and older were randomly selected from the Center for Medicare Services (CMS) lists in all four states. Controls were frequency matched to cases on ethnicity and 5-year age distribution. A total of 913 Hispanic, 23 American Indian, and 1669 NHW controls completed the interview and body measurements. DNA from blood samples was extracted for 1,850 cases (606 Hispanics, 1,244 NHWs) and 2,057 controls (728 Hispanics, 1,329 NHWs).

The Mexico Breast Cancer Study consisted of Hispanic women between 28 and 74 years of age, living in one of three states, Monterrey, Veracruz and Mexico City, for the past 5 years [20]. Cases newly diagnosed with in situ or invasive breast cancer between January 2004 and December 2007 were identified at 12 participating hospitals from three main health care systems in Mexico. Using a probabilistic multi-stage design, controls were randomly selected from the catchment areas of the participating hospitals. A total of 1,000 cases and 1,074 controls completed an in-person interview and body size measurements, and DNA was extracted from 85 and 96 % respectively.

The San Francisco Bay Area Breast Cancer Study (SFBCS) included Hispanic and NHW women between the ages of 35 and 79 years from the San Francisco Bay Area [21, 22]. Cases newly diagnosed with invasive breast cancer between April 1995 and April 2002 were identified through the Greater Bay Area Cancer Registry, and controls were selected by random-digit dialing (RDD) and frequency matched based on ethnicity and 5-year age distribution of cases. A total of 1,715 cases and 2,108 controls completed an in-person interview on breast cancer risk factors in English or Spanish and body size measurements. DNA from blood or mouthwash samples was available for 1,105 cases (793 Hispanics, 312 NHWs) and 1,318 controls (998 Hispanics, 320 NHWs).

Data harmonization

Interview data were harmonized across the three studies [18]. The main variables for harmonization were selected based on study hypotheses and the genetic pathways of interest. The present analyses included body mass index (BMI, kg/m^2) calculated as self-reported weight during the referent year (or more distantly recalled weight if referent year weight was not available or measured weight if neither were available) divided by measured height squared, parity (number of live births and stillborn pregnancies), age at first live birth or still birth, self-reported ethnicity in the U.S. studies (all women in Mexico were considered Hispanic), and highest level of education. The referent year was defined as the calendar year prior to diagnosis for cases and selection into the study for controls.

Genetic data

DNA was extracted from either whole blood (n = 7,286) or mouthwash (n = 637) samples. Whole genome amplification (WGA) was applied to the mouthwash-derived samples prior to genotyping. A tagSNP approach was used to characterize variation across candidate genes. TagSNPs were selected as follows: linkage disequilibrium (LD) blocks were defined using a Caucasian LD map and an r^2 = 0.8; minor allele frequency (MAF) >0.1; range = −1,500 bps from the initiation codon to +1,500 bps from the termination codon; and 1 SNP/LD bin. A total of 104 Ancestral Informative Markers (AIMs) were used to distinguish European and Native American ancestry in the study population [18]. All markers were genotyped using a multiplexed bead array assay format based on GoldenGate chemistry (Illumina, San Diego, California). A genotyping call rate of 99.93 % was attained (99.65 % for WGA samples). We included 132 internal replicates that were blinded representing 1.6 % of the sample set. The duplicate concordance rate was 99.996 % as determined by 193,297 matching genotypes among sample pairs [18].

In the current analysis, we examined 25 *TCF7L2* polymorphisms: rs176632, rs290489, rs1028629, rs1225404, rs2094405, rs3750804, rs3750805, rs3814570, rs3814572, rs4918796, rs6585206, rs7081062, rs7085532, rs7094463, rs7900150, rs7903146, rs7903424, rs7919185, rs10749127, rs10885399, rs10885410, rs11196174, rs11196199, rs12255372, and rs17685538. Online supplement 1 describes the *TCF7L2* polymorphisms in detail, including the minor allele frequencies (MAF) and adjusted Hardy–Weinberg equilibrium (HWE) p values. Online supplement 2 provides genotype and haplotype frequencies by ethnicity and case–control status. Online supplement 3 describes the LD between all 25 *TCF7L2* polymorphisms by self-reported ethnicity.

Tumor characteristics

Information on ER and PR status was obtained from the cancer registries in New Mexico, Utah, Colorado, Arizona, and California for 979 (68 %) NHW cases and 958 (75 %) Hispanic cases. These data were not available for Mexico.

Statistical methods

STRUCTURE was used to compute individual ancestry for each study participant assuming two founding populations [23, 24]. Descriptive statistics were calculated for all covariates and t tests and Chi-square tests were used to compare groups. Associations of *TCF7L2* polymorphisms with breast cancer risk were stratified by ethnicity, genetic ancestry, history of diabetes, BMI by menopausal status, and ER/PR status. Haplotype analysis was conducted using PROC haplotype in SAS, which uses the expectation–maximization (EM) algorithm to estimate the maximum likelihoods of haplotype frequencies based on the multilocus sample of the genotypes under the HWE assumption [25]. Using the linkage equilibrium method for initialization of estimated haplotype frequencies, SAS outputs all the haplotype combinations for each individual as probability scores based on their genotypes. The following SNPs were determined to have close base pair positions and yielded signals for strong crude associations with breast cancer risk: rs7081062, rs7903146, rs7900150, and rs11196199. Triplicates were then constructed based on the combination of rs7081062, rs7903146, and rs7900150 and for rs7903146, rs7900150, and rs11196199. Haplotype probabilities were categorized into probability for each subject and were included in the regression models [26]. Online supplement 2 describes these haplotype combinations and their frequencies by case–control status and ethnicity. The homozygous wildtypes for each polymorphism were used as the referent categories. Using co-dominant models, genotype associations for all *TCF7L2* SNPs were estimated as OR with 95 % CIs by unconditional logistic regression with adjustments for age and study center. Based on initial assessment of the co-dominant associations, dominant models and haplotypes were also examined.

Potential confounders included BMI, menopausal status, history of diabetes, percentage of genetic admixture, parity, oral contraceptive use, education, family history of breast cancer, age at menarche, history of hormone therapy use, physical activity, calories consumed per day, and smoking status (ever or never). These were included in multivariable models if their univariate *p* values were ≤0.20 and if they produced a change in the point estimate for the main effects of the *TCF7L2* genotypes of ≥10 % [27]. Interactions between *TCF7L2* variants with ethnicity, genetic ancestry, BMI by menopausal status, and history of diabetes were assessed using the likelihood-ratio test comparing the model including an interaction term with a reduced model without the term.

Women were classified as either pre-menopausal or post-menopausal based on self-reported responses to questions on menstrual history. Women who reported menstruation during the referent year were classified as pre-menopausal. The classification for post-menopausal women was established by using criteria provided by each individual study. If women were taking hormonal therapy (HT) and still having periods and were at or above the 95th percentile of age for ethnicity of those who reported having a natural menopause among their study site, they were classified as post-menopausal. This age was 58 for NHW and 56 for Hispanics in the 4-CBCS, age 54 in the Mexico Breast Cancer Study, and 55 for NHW and 56 for Hispanics in the SFBCS.

Multinomial logistic regression models were constructed to evaluate the associations between *TCF7L2* genotypes/haplotypes and breast cancer risk by ER/PR status [28, 29]. Since the Mexico Breast Cancer Study did not have data on ER/PR status, those subjects were excluded from the multinomial regression analyses.

Results were adjusted for multiple comparisons taking into account tagSNPs within the gene using the step-down Bonferroni correction (i.e., Holm's method) based on the effective number of independent SNPs as determined using the SNP spectral decomposition method proposed by Nyholt [30] and modified by Li and Ji [31]. The interaction p values, based on 1-df likelihood-ratio tests, were adjusted using the step-down Bonferroni correction or the Holm's test [32]. We considered an adjusted *p* value of 0.10 or less as potentially important for main effects and a Holm's *p* value of 0.15 or less for interactions. All data analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 7,733 breast cancer cases and controls were included in these analyses: 61 % were Hispanic and 39 % were NHW. More Hispanic cases were diagnosed with ER−/PR− tumors than NHW (23.2 vs. 18.3 %). Hispanic cases were more likely to be obese (BMI ≥ 30 kg/m^2) than NHW cases (39.7 vs. 24.8 %), and also had a significantly higher prevalence of Type 2 diabetes compared to NHW cases (16.6 vs. 7.2 %) (Table 1).

Of the 25 *TCF7L2* SNPs and 14 haplotypes evaluated, four polymorphisms and one haplotype were significantly associated with breast cancer risk (Table 2). Increased risk was associated with the TT genotype of rs7903146 (OR, 1.24; 95 % CI 1.03–1.49; $p = 0.0369$, $p_{adj} = 0.0474$), the dominant model of rs3750805 (AT/TT vs. AA) (OR, 1.15; 95 % CI 1.03–1.28; $p = 0.0098$, $p_{adj} = 0.0420$) and the AA genotype of rs7900150 (OR, 1.23; 95 % 1.07–1.42; $p = 0.0139$, $p_{adj} = 0.0457$). The CC genotype of rs1225404 was inversely associated with breast cancer risk (OR, 0.82; 95 % CI 0.70–0.94; $p = 0.0149$, $p_{adj} = 0.0457$). Although the association was of borderline significance, the TT genotype of rs12255372 was positively associated (OR, 1.20; 95 % CI 0.99–1.46). There was no evidence for effect modification or significant interaction after stratification by self-reported ethnicity and by levels of genetic admixture (data not shown).

When stratified on diabetes history, there was a positive association with the TT genotype of rs3750804 in women with a history of diabetes (OR, 2.46; 95 % CI 1.28–4.73), but no association among women without a history (OR, 1.06; 95 % CI 0.85–1.32) ($p_{interaction}$ = 0.0043; p_{adj} = 0.0086). The dominant mode of inheritance for rs3814570 (CC vs. CT/TT) was inversely associated with risk among women with a history of diabetes (OR, 0.76; 95 % CI 0.58–0.99), while there was a small increased risk among women without diabetes history (OR, 1.13; 95 % CI 1.02–1.26) ($p_{interaction}$ = 0.0099; p_{adj} = 0.0099) (Table 3).

We also examined whether the association between breast cancer and *TCF7L2* was modified by BMI and menopausal status (data not shown). There was a significant three-way interaction between rs17685538, BMI and menopausal status (p = 0.004). Although the p values for interactions were not significant for rs7900150 and rs1028629, the AA genotype of rs7900150 (OR, 1.93; 95 % CI 1.22–3.06) and the TT genotype of rs1028629 (OR, 3.15; 95 % CI 1.09–9.10) were associated with increased breast cancer risk among obese (BMI ≥ 30 kg/m^2) pre-menopausal women. The CC genotype of rs4918796 (OR, 1.92; 95 % CI 1.18–3.10) and 2 copies of the A-T-A haplotype from the SNP combination between rs7081062, rs7903146, and rs7900150 (OR, 1.61; 95 % CI 1.05–2.47) were associated with increased breast cancer risk among obese, post-menopausal women.

Table 4 shows associations of *TCF7L2* SNPs/haplotypes with breast cancer risk by ER/PR tumor phenotype. The TT genotype of rs7903143 (p_{trend} = 0.0798, p_{adj} = 0.2186) was associated with an increased risk for ER−/PR− tumors (OR, 1.56; 95 % CI 1.07–2.27). The following polymorphisms and haplotypes were also associated with ER−/PR− breast cancer with OR ranging from 1.59 to 2.39: rs7900150 (p_{trend} = 0.0271; p_{adj} = 0.1014), rs10749127 (p_{trend} = 0.0057; p_{adj} = 0.0327), and haplotypes A-T-A and T-A-G from the SNP combination between rs7081062, rs7903146, and rs7900150. Although their unadjusted p values did not reach statistical significance, the TT genotype of rs3814570 (OR, 1.49; 95 % CI 1.04–2.14) and the dominant model (CT/TT vs. CC) of rs3750804 (OR, 1.25; 95 % CI 1.01–1.54) were also associated with an increased risk for ER−/PR− breast cancer. The CC genotype of rs4918796 (p_{trend} = 0.0068; p_{adj} = 0.0327) was associated with an increased risk for ER−/PR+ tumors (OR, 4.78; 95 % CI 1.89–12.12) and ER+/PR+ tumors (OR, 1.62; 95 % CI 1.20–2.20) (Table 4).

Discussion

In this large sample of Hispanic and NHW women from the BCHDS, four polymorphisms, including rs7903146, and one haplotype were significantly associated with breast cancer risk after adjusting for multiple comparisons. Although we did not find significant interactions with ethnicity or by genetic admixture, our data suggest that the associations of rs3750804 and rs3814570 with breast cancer risk may be modified by diabetes history. Some associations may have been influenced by obesity and menopausal status also. Lastly, results suggest that the associations of several *TCF7L2* polymorphisms and two haplotypes may differ by ER and PR status.

We evaluated the associations of the more-widely studied polymorphisms, rs7903146 and rs12255372, as well as 23 other SNPs to better characterize associations across the gene. Consistent with our findings, Naidu et al. reported that the T allele of rs12255372 (TT genotype, OR, 1.574; 95 % CI 0.829–2.987); GT/TT, OR, 1.365; 95 % CI 0.989–1.883) was not associated with risk of breast cancer. However, carriers of the rs7903146 T allele (OR, 1.316; 95 % CI 1.022–1.695) and CT/TT genotypes, (OR, 1.419; 95 % CI 1.027–1.960) had an increased risk [17]. Burwinkel et al. [15] examined the association of rs12255372 with familial breast cancer risk and reported that the T allele was significantly, positively associated (OR, 1.19; 95 % CI 1.01–1.42, p = 0.04) [15]. In contrast, Goode et al. [16] found

no overall association (OR, 1.04; 95 % CI 0.89–1.22) [16]. However, in sub-group analyses, associations were observed in pre-menopausal women (OR, 1.46; 95 % CI 0.99–2.15; $p = 0.06$), and those with HER2 positive (OR, 1.48; 95 % CI 1.00–2.01; $p = 0.05$) or triple negative (OR, 2.01; 95 % CI 1.10–3.67; $p = 0.02$) breast cancer [16]. Although our study was unable to assess the association between *TCF7L2* and HER2 positive or triple negative breast cancers, given incomplete data on HER2 status, results suggests that several of the polymorphisms and haplotypes were significantly associated with the ER−/PR− tumor phenotype.

Specific variants of *TCF7L2* have been reported to be associated with risk of diabetes [2, 4, 5]. Although the underlying mechanisms are unclear, studies suggest that the gene may regulate glucagon-like peptide 1 (GLP-1) through the Wnt-signaling pathway [5]. The association between diabetes and breast cancer risk has received increased attention in epidemiological research, but findings are mixed [33–42]. Based on the *TCF7L2* gene's influence on diabetes, and its potential to increase breast cancer risk, we tested for interaction effects between women who had a history of diabetes and women who did not. We did not find significant interaction effects for variants rs7903146 and rs12255372, the two SNPs that have been implicated as the major *TCF7L2* polymorphisms associated with diabetes. However, we identified two other variants, rs3750804 and rs3814570, that could further be explored for associations with diabetes and breast cancer risk.

The mechanism underlying the association between *TCF7L2* and breast cancer has not been established, although the Wnt/β-catenin pathway has been implicated [9, 10]. In normal cells, the levels of free cytosolic β-catenin are maintained, due to their degradation by the APC, AXIN and kinase GSK3β complex. This multicomponent complex phosphorylates β-catenin on N-terminal residues and targets the protein for ubiquitination and proteolysis [10, 43]. However, stimulation of the Wnt-pathway with a ligand inhibits the activity of the complex, and β-catenin is less phosphorylated and ubiquitinated, leading to an accumulation of β-catenin in the cytosol and increased entry of β-catenin into the nucleus [10, 43]. Once in the nucleus, β-catenin combines with transcription factors of the TCF/LEF1 family and forms a complex that stimulates the expression of certain target genes, including cyclin D1 and c-*myc* [10]. Other target genes for *TCF7L2* have been found for breast cancer including osteopontin (OPN), monocyte chemotactic protein-1 (MCP-1/CCL2), and RAD6B. OPN functions in neoplastic transformation, malignant cell attachment, and migration and high serum levels of OPN have been found to be associated with metastasis [1].

Continuous stimulation of the Wnt-signaling pathway leads to APC mutations that result in increased expression of the β-catenin protein and higher β-catenin-Tcf transcriptional activity. Some have investigated the role of mutations in the β-catenin, APC, and/or AXIN in breast cancer carcinogenesis, but few have reported significant results. The best evidence implicates mutations in APC [9]. It is not clear if the mutations in the Wnt-signaling pathway components directly contribute to the β-catenin levels, as increased levels of β-catenin-Tcf transcriptional activity have been found in breast cancer cell lines [9].

Our study has several strengths. It included a large sample size of over 3,500 cases and 4,200 controls from three population-based case–control studies conducted in the United States and Mexico, and 1,937 cases with available data on tumor hormone receptor status. Another important strength was the large number of Hispanic women included in the analyses. Previous studies with *TCF7L2* and breast cancer did not include Hispanic women [15–17]. In addition to evaluating ethnic differences in associations between Hispanics and NHWs, we were able to account for genetic admixture in our analyses. We previously demonstrated that women with more Native American versus more European ancestry have lower risk of breast cancer [18, 44]. Adjusting for genetic ancestry within admixed

populations may also adjust for other underlying genetic factors that influence breast cancer risk.

While we accounted for multiple comparisons, this adjustment does not completely eliminate false positive associations. Therefore, replication of these results, particularly the interaction effects by diabetes history, is needed. Another limitation is the lack of tumor phenotype data for the Mexico Breast Cancer Study, which contributed 816 Hispanic cases and 994 Hispanic controls. Hispanic women with breast cancer are more likely to have ER−/PR− tumors [45], and inclusion of these women in our multinomial logistic regression analysis might have strengthened our results by tumor phenotype.

In summary, using a tagSNP approach, our results suggest that there is a significant association between the *TCF7L2* gene and risk of breast cancer regardless of ethnicity and/or Native American ancestry. A novel finding is potential effect modification by history of diabetes for *TCF7L2* polymorphisms rs3750804 and rs3814570. We also identified several variants that may be associated with risk for the ER−/PR− tumor phenotype. Although we did not find significant interactions by Hispanic ethnicity or by genetic admixture, additional research is needed to elucidate factors that contribute to racial/ethnic disparities in breast cancer. Future research on breast cancer genetics should involve identifying genetic differences by race and ethnicity for breast cancer risk, prognosis, and survival. Such findings could illuminate new pathways for breast cancer treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Ravindranath A, O'Connell A, Johnston PG, El-Tanani MK. The role of LEF/TCF factors in neoplastic transformation. Curr Mol Med. 2008; 8(1):38–50. [PubMed: 18289012]

2. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006; 38(3):320–323.10.1038/ng1732 [PubMed: 16415884]
3. Bodhini D, Radha V, Dhar M, Narayani N, Mohan V. The rs12255372(G/T) and rs7903146(C/T) polymorphisms of the TCF7L2 gene are associated with type 2 diabetes mellitus in Asian Indians. Metab Clin Exp. 2007; 56(9):1174–1178.10.1016/j.metabol.2007.04.012 [PubMed: 17697858]
4. Tong Y, Lin Y, Zhang Y, Yang J, Liu H, Zhang B. Association between TCF7L2 gene polymorphisms and susceptibility to type 2 diabetes mellitus: a large Human Genome Epidemiology (HuGE) review and meta-analysis. BMC Med Genet. 2009; 10:15.10.1186/1471-2350-10-15 [PubMed: 19228405]
5. Zhang C, Qi L, Hunter DJ, Meigs JB, Manson JE, van Dam RM, Hu FB. Variant of transcription factor 7-like 2 (TCF7L2) gene and the risk of type 2 diabetes in large cohorts of U.S. women and men. Diabetes. 2006; 55(9):2645–2648.10.2337/db06-0643 [PubMed: 16936216]
6. Korner A, Kiess W, Stumvoll M, Kovacs P. Polygenic contribution to obesity: genome-wide strategies reveal new targets. Front Horm Res. 2008; 36:12–36.10.1159/0000115335 [PubMed: 18230892]
7. Smith U. TCF7L2 and type 2 diabetes—we WNT to know. Diabetologia. 2007; 50(1):5–7.10.1007/s00125-006-0521-z [PubMed: 17102948]
8. Gebeshuber CA, Sladecek S, Grunert S. Beta-catenin/LEF-1 signalling in breast cancer–central players activated by a plethora of inputs. Cells Tissues Organs. 2007; 185(1–3):51–60.10.1159/000101303 [PubMed: 17587808]
9. Brown AM. Wnt signaling in breast cancer: have we come full circle? Breast Cancer Res. 2001; 3(6):351–355. [PubMed: 11737884]
10. Howe LR, Brown AM. Wnt signaling and breast cancer. Cancer Biol Ther. 2004; 3(1):36–41. [PubMed: 14739782]
11. Polakis P. Wnt signaling in cancer. Cold Spring Harbor Perspect Biol. 2012; 4(5)10.1101/cshperspect.a008052
12. Chung GG, Zerkowski MP, Ocal IT, Dolled-Filhart M, Kang JY, Psyrri A, Camp RL, Rimm DL. Beta-catenin and p53 analyses of a breast carcinoma tissue microarray. Cancer. 2004; 100(10):2084–2092.10.1002/cncr.20232 [PubMed: 15139049]
13. Geyer FC, Lacroix-Triki M, Savage K, Arnedos M, Lambros MB, MacKay A, Natrajan R, Reis-Filho JS. Beta-catenin pathway activation in breast cancer is associated with triple-negative phenotype but not with CTNNB1 mutation. Mod Pathol. 2011; 24(2): 209–231.10.1038/modpathol.2010.205 [PubMed: 21076461]
14. Khramtsov AI, Khramtsova GF, Tretiakova M, Huo D, Olopade OI, Goss KH. Wnt/beta-catenin pathway activation is enriched in basal-like breast cancers and predicts poor outcome. Am J Pathol. 2010; 176(6):2911–2920.10.2353/ajpath.2010.091125 [PubMed: 20395444]
15. Burwinkel B, Shanmugam KS, Hemminki K, Meindl A, Schmutzler RK, Sutter C, Wappenschmidt B, Kiechle M, Bartram CR, Frank B. Transcription factor 7-like 2 (TCF7L2) variant is associated with familial breast cancer risk: a case-control study. BMC Cancer. 2006; 6:268.10.1186/1471-2407-6-268 [PubMed: 17109766]
16. Goode EL, Szabo C, Prokunina-Olsson L, Vierkant RA, Fredericksen ZS, Collins FS, White KL, Schmidt M, Fridley BL, Couch FJ. No association between a candidate TCF7L2 variant and risk of breast or ovarian cancer. BMC Cancer. 2009; 9:312.10.1186/1471-2407-9-312 [PubMed: 19732438]
17. Naidu R, Yip CH, Taib NA. Genetic variations in transcription factor 7-like 2 (TCF7L2) gene: association of TCF7L2 rs12255372(G/T) or rs7903146(C/T) with breast cancer risk and clinico-pathological parameters. Med Oncol. 201110.1007/s12032-011-9837-8
18. Slattery M, John E, Torres-Mejia G, Lundgreen A, Herrick J, Baumgartner K, Hines L, Stern M, Wolff R. Genetic variation in genes involved in hormones, inflammation, and energetic factors and breast cancer risk in an admixed population. Carcinogenesis. 201210.1093/carcin/bgs163

19. Slattery ML, Sweeney C, Edwards S, Herrick J, Baumgartner K, Wolff R, Murtaugh M, Baumgartner R, Giuliano A, Byers T. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. Breast Cancer Res Treat. 2007; 102(1):85–101.10.1007/s10549-006-9292-y [PubMed: 17080310]
20. Angeles-Llerenas A, Ortega-Olvera C, Perez-Rodriguez E, Esparza-Cano JP, Lazcano-Ponce E, Romieu I, Torres-Mejia G. Moderate physical activity and breast cancer risk: the effect of menopausal status. Exerc Sport Sci Rev. 2010; 21(4):577–586.10.1007/s10552-009-9487-8
21. John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in a multiethnic population: the San Francisco Bay area breast cancer study. Cancer Epidemiol Biomark Prev. 2003; 12(11 Pt 1):1143–1152.
22. John EM, Phipps AI, Davis A, Koo J. Migration history, acculturation, and breast cancer risk in Hispanic women. Cancer Epidemiol Biomark Prev. 2005; 14(12):2905–2913.10.1158/1055-9965.EPI-05-0483
23. Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics. 2003; 164(4):1567–1587. [PubMed: 12930761]
24. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. Genetics. 2000; 155(2):945–959. [PubMed: 10835412]
25. Long JC, Williams RC, Urbanek M. An E–M algorithm and testing strategy for multiple-locus haplotypes. Am J Hum Genet. 1995; 56(3):799–810. [PubMed: 7887436]
26. Zaykin DV, Westfall PH, Young SS, Karnoub MA, Wagner MJ, Ehm MG. Testing association of statistically inferred haplotypes with discrete and continuous traits in samples of unrelated individuals. Hum Hered. 2002; 53(2):79–91. [PubMed: 12037407]
27. Hosmer, D.; Lemeshow, S. Applied logistic regression. Wiley; New York: 1989.
28. Flom, PL. Multinomial and ordinal logistic regression using PROC LOGISTIC. Vol. 9. National Development and Research Institutes, Inc; New York: 2010.
29. Hosmer, DWaLS. Applied logistic regression. 2. Wiley; New York: 2000.
30. Nyholt DR. A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. Am J Hum Genet. 2004; 74(4):765–769.10.1086/383251 [PubMed: 14997420]
31. Li J, Ji L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. Heredity. 2005; 95(3): 221–227.10.1038/sj.hdy.6800717 [PubMed: 16077740]
32. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979; 6(2):65–70.
33. Arif JM, Al-Saif AM, Al-Karrawi MA, Al-Sagair OA. Causative relationship between diabetes mellitus and breast cancer in various regions of Saudi Arabia: an overview. Asian Pac J Cancer Prev. 2011; 12(3):589–592. [PubMed: 21627349]
34. Khachatryan L, Scharpf R, Kagan S. Influence of diabetes mellitus type 2 and prolonged estrogen exposure on risk of breast cancer among women in Armenia. Health Care Women Int. 2011; 32(11): 953–971.10.1080/07399332.2011.569041 [PubMed: 21978143]
35. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007; 121(4): 856–862.10.1002/ijc.22717 [PubMed: 17397032]
36. Liao S, Li J, Wei W, Wang L, Zhang Y, Wang C, Sun S. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pac J Cancer Prev. 2011; 12(4): 1061–1065. [PubMed: 21790252]
37. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. Diabetes mellitus and breast cancer: a retrospective population-based cohort study. Breast Cancer Res Treat. 2006; 98(3): 349–356.10.1007/s10549-006-9172-5 [PubMed: 16541321]
38. Michels KB, Solomon CG, Hu FB, Rosner BA, Hankinson SE, Colditz GA, Manson JE. Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. Diabetes Care. 2003; 26(6):1752–1758. [PubMed: 12766105]
39. Schott S, Schneeweiss A, Sohn C. Breast cancer and diabetes mellitus. Exp Clin Endocrinol Diabetes. 2010; 118(10):673–677.10.1055/s-0030-1254116 [PubMed: 20533174]

40. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev. 2007; 8(5):395–408.10.1111/j.1467-789X.2007.00396.x [PubMed: 17716297]

41. Wolf I, Sadetzki S, Gluck I, Oberman B, Ben-David M, Papa MZ, Catane R, Kaufman B. Association between diabetes mellitus and adverse characteristics of breast cancer at presentation. Eur J Cancer. 2006; 42(8):1077–1082.10.1016/j.ejca.2006.01.027 [PubMed: 16574404]

42. Rollison DE, Giuliano AR, Sellers TA, Laronga C, Sweeney C, Risendal B, Baumgartner KB, Byers T, Slattery ML. Population-based case-control study of diabetes and breast cancer risk in Hispanic and non-Hispanic White women living in US southwestern states. Am J Epidemiol. 2008; 167(4):447–456.10.1093/aje/kwm322 [PubMed: 18033764]

43. MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell. 2009; 17(1): 9–26.10.1016/j.devcel.2009.06.016 [PubMed: 19619488]

44. Fejerman L, John EM, Huntsman S, Beckman K, Choudhry S, Perez-Stable E, Burchard EG, Ziv E. Genetic ancestry and risk of breast cancer among U.S. Latinas. Cancer Res. 2008; 68(23): 9723–9728.10.1158/0008-5472.CAN-08-2039 [PubMed: 19047150]

45. Ooi SL, Martinez ME, Li CI. Disparities in breast cancer characteristics and outcomes by race/ethnicity. Breast Cancer Res Treat. 2011; 127(3):729–738.10.1007/s10549-010-1191-6 [PubMed: 21076864]

Table 1

Characteristics of study population, stratified by ethnicity and case–control status, The Breast Cancer Health Disparities Study (n = 7,733)

	Non-Hispanic Whites (n = 3,030)				p Value[a]	Hispanics (n = 4,703)				p Value[a]	p Value[b]
	Cases		Controls			Cases		Controls			
	No.	%	No.	%		No.	%	No.	%		
Total subjects	1,431		1,599			2,093		2,610			
Study site											
4-CBCS	1,177	82.3	1,335	83.5	0.37	579	27.7	736	28.2	0.94	<0.001
Mexico	–		–			816	39.0	994	38.1		
SFBCS	254	17.8	264	16.5		698	33.4	880	33.7		
Menopausal status											
Pre-menopausal	475	34.1	494	31.5	0.13	831	41.2	1,027	40.7	0.71	<0.001
Post-menopausal	919	66.9	1,075	68.5		1,186	58.8	1,499	59.3		
Body mass index (kg/m^2)[c]											
<25	651	46.1	699	44.4	0.30	482	23.4	453	17.6	<0.001	<0.001
25–29.9	411	29.1	465	29.5		762	37.0	951	36.9		
30+	350	24.8	412	26.1		818	39.7	1,172	45.5		
History of type 2 diabetes											
Yes	91	7.2	122	8.6	0.20	308	16.6	386	16.6	0.98	<0.001
No	1,166	92.8	1,299	91.4		1,548	83.4	1,945	83.4		
1st degree family history of breast cancer											
No	1071	77.4	1,289	84.5	<0.001	1,799	88.1	2,326	91.8	<0.001	<0.001
Yes	312	22.6	237	15.5		244	11.9	208	8.2		
Estrogen/progesterone receptor (ER/PR) status											
ER+/PR+	670	68.4	–		–	595	62.1	–		–	0.002
ER+/PR−	115	11.8	–			114	11.9	–			
ER−/PR+	15	1.5	–			27	2.8				
ER−/PR−	179	18.3	–			222	23.2				
Percentage of Native American genetic admixture											
≤0.28	1,420	99.2	1,591	99.5	0.21	276	13.2	280	10.7	0.001	<0.001
0.28–0.70	7	0.5	7	0.4		1,373	65.6	1,697	65.0		

	Non-Hispanic Whites (n = 3,030)				p Value[a]	Hispanics (n = 4,703)				p Value[a]	p Value[b]
	Cases		Controls			Cases		Controls			
	No.	%	No.	%		No.	%	No.	%		
>0.70	4	0.3	1	0.1		444	21.2	633	24.3		
History of menopausal hormone use											
Yes	795	69.2	899	69.2	0.98	616	32.5	713	29.5	0.03	<0.001
No	354	30.8	401	30.8		1280	67.5	1,704	70.5		
Education level											
Less than high school	71	5.0	79	5.0	0.57	1088	52.8	1,538	60.2	<0.001	<0.001
High school grad/GED	284	20.1	338	21.4		377	18.3	419	16.4		
College education	1,059	74.9	1168	73.6		594	29.0	597	23.4		
Parity											
Nulliparous	249	17.6	248	15.7	0.001	225	10.8	181	7.0	<0.001	<0.001
1–2	622	44.0	638	40.3		774	37.2	790	30.5		
3–4	441	31.2	529	33.4		729	35.0	997	38.4		
5+	102	7.2	167	10.6		353	17.0	626	24.1		

	Mean	(SD)	Mean	(SD)	p Value[d]	Mean	(SD)	Mean	(SD)	p Value[d]	p Value[e]
Age (years)	55.9	11.2	56.7	12.3	0.05	52.7	10.6	52.3	10.8	0.25	<0.001

Missing information: education, n = 121; parity, n = 62; menopausal status, n = 227; menopausal hormone use, n = 971; family history of breast cancer, n = 247; history of diabetes, n = 868; body mass index, n = 107; estrogen receptor status, n = 5797 (cases only)

[a] Case–control comparison within ethnicity. p Values from Chi-square tests

[b] Ethnic group comparison, regardless of case–control status. Mantel–Haenszel Chi-square p values from Chi-square tests

[c] Body mass index (BMI) in referent year calculated as kilograms (kg)/meters $(m)^2$

[d] Case–control comparison within ethnicity. p Values from t tests

[e] Ethnic group comparison, regardless of case–control status. p Values from t tests

Table 2

Significant associations between *TCF7L2* SNPs and breast cancer risk, The Breast Cancer Health Disparities Study

TCF7L2	Genotypes	Overall			
		Cases/controls	OR (95 % CI)	Wald *P*	P_{adj}
rs1225404	TT	1561/1735	1.00	0.0149	0.0457
	CT	1564/1921	0.92 (0.83–1.01)		
	CC	399/552	0.82 (0.70–0.94)		
rs3750805	AA	2663/3292	1.00	0.0098	0.0420
	AT/TT	861/917	1.15 (1.03–1.28)		
rs7900150	TT	1377/1780	1.00	0.0139	0.0457
	TA	1559/1849	1.04 (0.94–1.16)		
	AA	587/579	1.23 (1.07–1.42)		
rs7903146	CC	1961/2483	1.00	0.0369	0.0474
	CT	1304/1476	1.09 (0.99–1.20)		
	TT	258/250	1.24 (1.03–1.49)		
rs12255372[a]	GG	2041/2552	1.00	0.1567	0.1567
	GT	1252/1431	1.05 (0.95–1.16)		
	TT	229/226	1.20 (0.99–1.46)		
Haplotype					
rs7081062					
rs7903146					
rs7900150	Copies				
A-T-A	0	3088/3790	1.00	0.0155	
	1	211/215	1.16 (0.95–1.42)		
	2	225/204	1.30 (1.06–1.58)		

OR (odds ratios) and 95 % confidence interval (CI) adjusted for age, study, and genetic admixture

[a]rs12255372 is presented to compare its main effects with other breast cancer studies

Table 3

Interaction between *TCF7L2*, history of Type 2 diabetes, and breast cancer risk, The Breast Cancer Health Disparities Study

TCF7L2	**Genotype**	**Diabetes history Cases = 399/controls = 508 OR (95 % CI)**	**No diabetes history Cases = 2714/controls = 3244 OR (95 % CI)**	$P_{interaction}$	$P_{(adj)}$
rs3750804	CC	1.00	1.00	0.0043	0.0086
	CT	0.81 (0.61–1.08)	1.09 (0.97–1.21)		
	TT	2.46 (1.28–4.73)	1.06 (0.85–1.32)		
rs3814570	CC	1.00	1.00	0.0099	0.0099
	CT/TT	0.76 (0.58–0.99)	1.13 (1.02–1.26)		

OR (odds ratios) and 95 % confidence interval (CI) adjusted for age, study, BMI in referent year, and genetic admixture

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Table 4

Associations of *TCF7L2* polymorphisms with breast cancer risk, by ER/PR status, The Breast Cancer Health Disparities Study

TCF7L2	**Controls *N* = 3,215 Genotypes/copies**	**ER+/PR+ *N* = 1,265 cases OR (95 % CI)**	**ER+/PR− *N* = 229 cases OR (95 % CI)**	**ER−/PR+ *N* = 42 cases OR (95 % CI)**	**ER−/PR− *N* = 401 cases OR (95 % CI)**
rs3750804	CC	1.00	1.00	1.00	1.00
	CT/TT	1.11 (0.97–1.26)	1.02 (0.77–1.34)	0.95 (0.51–1.77)	1.25 (1.01–1.54)
rs3814570	CC	1.00	1.00	1.00	1.00
	CT	1.15 (1.00–1.32)	1.07 (0.80–1.41)	0.68 (0.35–1.34)	1.08 (0.86–1.34)
	TT	1.00 (0.77–1.30)	1.23 (0.75–2.01)	0.83 (0.25–2.78)	1.49 (1.04–2.14)
rs4918796	TT	1.00	1.00	1.00	1.00
	TC	1.12 (0.97–1.29)	1.08 (0.81–1.45)	1.09 (0.54–2.21)	1.00 (0.80–1.26)
	CC	1.62 (1.20–2.20)	0.96 (0.46–2.02)	4.78 (1.89–12.12)	0.81 (0.44–1.50)
rs7900150	TT	1.00	1.00	1.00	1.00
	TA	1.06 (0.91–1.23)	1.10 (0.80–1.50)	1.06 (0.52–2.13)	1.08 (0.85–1.38)
	AA	1.19 (0.98–1.44)	1.43 (0.97–2.11)	1.31 (0.53–3.20)	1.59 (1.18–2.14)
rs7903146	CC	1.00	1.00	1.00	1.00
	CT	1.11 (0.97–1.28)	1.27 (0.96–1.69)	1.06 (0.54–2.07)	1.10 (0.88–1.38)
	TT	1.25 (0.98–1.61)	1.08 (0.63–1.87)	2.00 (0.74–5.43)	1.56 (1.07–2.27)
rs10749127	TT	1.00	1.00	1.00	1.00
	TC/CC	0.88 (0.77–1.00)	0.83 (0.64–1.09)	1.75 (0.93–3.31)	1.25 (1.02–1.55)
Haplotype					
rs7081062					
rs7903146					
rs7900150					
A-T-A	0	1.00	1.00	1.00	1.00
	1	1.10 (0.84–1.44)	1.71 (1.07–2.73)	1.36 (0.41–4.52)	1.26 (0.83–1.91)
	2	1.30 (1.00–1.68)	1.09 (0.62–1.92)	1.90 (0.66–5.44)	1.50 (1.01–2.24)
T-A-G	0	1.00	1.00	1.00	1.00
	1 + 2	1.07 (0.60–1.92)	2.91 (1.33–6.36)	too few	2.39 (1.20–4.75)

OR (odds ratios) and 95 % confidence interval (CI) adjusted for age, study, BMI in referent year, and genetic admixture ER/PR data are compared to 3,215 controls from the 4-CBCS and SFBCS with available data on ER/PR status